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SPOTLIGHT COMMENTARY

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Spotlight Commentary: Model-informed precision dosing must demonstrate improved patient outcomes

Fifty years ago, Louis Sheiner published a seminal paper demonstrating that a computer-based mathematical model could be used to predict warfarin dose requirements.[1] The paper is remarkable in scope. It includes details of the model development and application as well as an evaluation of dose predictions against the gold standard at the time (expert opinion). Despite its obvious utility, as far as we know, Sheiner's dosing tool was never validated for use in practice. Therefore, the publication represents a ground-breaking pharmacometric output, with little to show in terms of clinical uptake or direct impact on patient care.

Fifty year on, pharmacometrics has grown as a discipline and is now an integral part of most drug development programmes. Model-based analyses are routinely used in the industry to inform study designs, to understand the relationship between drug exposure and response (efficacy and safety), and to support dosing requirements on the drug label. In the clinical setting, pharmacometrics research has focused largely on the development of models and dose prediction tools, including dose-banding tables[2] and decision-support underpinned by Bayesian algorithms.[3] However, widespread acceptance of pharmacometrics has been slow to develop in the clinical setting, and few model-based dosing tools have been widely implemented. The result is an overemphasis in the published literature on the production of new models and prediction tools but little in the way of concrete evidence to demonstrate that these outputs have a direct impact on clinical care. At best, published modelling outputs may demonstrate indirect evidence of a proposed clinical benefit, for example, using a simulation-based approach to show that plasma concentrations or biomarkers can be maintained within an optimal range. This important point has been the focus of much recent literature where a new acronym has emerged, "model-informed precision dosing (MIPD)".[4-6] MIPD refers to the use of pharmacometric outputs, ie, models, simulation, and Bayesian forecasting tools designed to predict the optimal dose of a drug for an individual patient. The goal is to improve efficacy while reducing the risk of toxicity. While interest in MIPD is gaining momentum amongst academics, there exist many challenges to address before pharmacometric outputs become routinely implemented in clinical practice.

A rudimentary form of MIPD is the use of plasma drug concentrations such as trough concentrations relative to a reference range to inform dose adjustments in support of patient care (therapeutic drug monitoring). Despite a substantial body of data suggesting that therapeutic drug monitoring might be useful for a large number of drugs, only a relatively small number are routinely monitored. A major reason for this is the shortage of assays that can quantify the concentration of the drugs in plasma samples and that have been approved for patient care by regulatory authorities. For those assays that have been approved, turnaround times are often (too) long. However, perhaps, the most important reason why drug concentration monitoring is not widely accepted is the general lack of clinical evidence generated from prospective randomised controlled trials that prove that therapeutic drug monitoring leads to optimisation of treatment in terms of efficacy and safety.

MIPD provides a means of predicting drug response and dose requirements in individual patients by quantifying and accounting for sources of variability between and within patients. Despite the obvious utility for clinical practice, we argue that MIPD will not be widely accepted by the clinical community nor routinely implemented across practice settings until modelling outputs can demonstrate important improvements in patient outcomes. Clinical trials to prospectively assess the clinical impact of MIPD tools have not been widely conducted to date (see Neely et al[7] and Joerger et al[8] for important exceptions). There are examples of MIPD outputs that have been implemented in local clinical settings but few examples of widespread implementation at a national or international scale (see the Dutch National Formulary[9] for an example of an important success story).

We are not suggesting that new modelling projects will not be warranted for some drugs and in certain population groups. Nor are we implying that all drugs will benefit from MIPD in practice. We are mainly concerned with those agents that demonstrate a narrow therapeutic range, where variability in response is difficult to predict, or where dose bands are complex or multidimensional. Indeed, the dose-concentration-response relationship for many commonly used agents may not be well understood. This means that suitable targets for plasma concentrations or other biomarkers have not been quantified. In addition, information on altered pharmacokinetics and pharmacodynamics in some patient groups (eg, children and pregnant women) may be lacking. However, we note that there are many well-studied agents with a large number of published models, often across patient groups and clinical settings (eg, tacrolimus[10]). In these situations, there may be a case for limiting the new modelling outputs in favour of

using models already available in the literature. Several recent publications have demonstrated the utility of meta-modelling and model-based meta-analysis methodologies for this purpose (see Claisse et al[11]).

We also acknowledge the challenges outlined by other commentators, particularly those related to the limited funds available for prospective testing and the regulatory issues associated with rolling out MIPD tools in practice.[4-6] Our view is simply that until direct evidence exists that MIPD outputs improve patient outcomes, it is unlikely that funding bodies, health authorities, and regulatory agencies will have much incentive to listen. If the clinical benefits are truly important, and this can be demonstrated in well-conducted trials, then the funding and regulatory bodies will have a much easier time taking MIPD seriously and the challenges become less imposing.

In this issue of the British Journal of Clinical Pharmacology, Zhang and colleagues[12] present a randomized clinical trial exploring the impact of model-based paclitaxel dosing compared to the standard body surface area (BSA) adjustment. The study was conducted in Chinese patients with advanced NSCLC, a population particularly at risk from haematological toxicities using the standard first-line platinum/paclitaxel chemotherapy. After the first cycle, patients were randomized to receive either standard 175 mg/m^2 doses of paclitaxel or individualized doses based on a target time above the paclitaxel plasma concentration of 0.05 μmol/L ($PTX_{Tc > 0.05}$) of 26 to 31 hours. Dose adjustments were conducting using a therapeutic drug monitoring and a model-based Bayesian dosing tool originally proposed by Joerger et al.[8] The authors found that paclitaxel doses were significantly lower in the model-based dosing group across cycles 2 to 4, with an average of 128 mg/m^2 compared to 161 mg/m^2 in the control arm. The primary safety endpoint of CTCAE grade 4 bone marrow toxicities was significantly reduced in the model-based dosing group overall (from 24% to 15%) and grade $\geq$ 2 neuropathy (from 21% to 8%). Efficacy endpoints such as objective response and disease control were not different between the study arms, while progression free-survival was longer in the model-based arm. Median overall survival did not differ between the study arms after about 2 years. In short, the authors appear to have successfully demonstrated that model-based paclitaxel dosing reduces the occurrence of severe neutropenia and paclitaxel-associated neuropathy without appreciable loss of efficacy.

High quality models for many drugs and population groups already abound in pharmacology. Many have been only validated at a theoretical level. However, implementation into practice requires comparative efficacy and/or safety compared to standard care and sometimes regulatory approval to guarantee quantification around safety and efficacy statements in the model. The results reported by Zhang et al are exactly the kind of data that is much needed for successful implementation of therapeutic drug monitoring and model-informed precision dosing.

COMPETING INTERESTS

There are no competing interests to declare.

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REFERENCES

1. Sheiner LB. Computer-aided long-term anticoagulation therapy. *Comput Biomed Res*. 1969;2(6):507–518.
2. Wright DFB, Duffull SB, Merriman TR, Dalbeth N, Barclay ML, Stamp LK. Predicting allopurinol response in patients with gout. *Br J Clin Pharmacol*. 2016;81(2):277–289.
3. Xue L, Holford NHG, Ding XL, et al. Theory-based pharmacokinetics and pharmacodynamics of S-and R-warfarin and effects on international normalized ratio: influence of body size, composition and genotype in cardiac surgery patients. *Br J Clin Pharmacol*. 2017;83(4):823–835.
4. Darwich AS, Ogungbenro K, Vinks AA, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther*. 2017;101(5):646–656.
5. Polasek TM, Rostami-Hodjegan A, Yim DS, et al. What does it take to make model-informed precision dosing common practice? Report from the 1st Asian symposium on precision dosing. *AAPSJ*. 2019;21(2):17. https://doi.org/10.1208/s12248-018-0286-6
6. Standing JF. Understanding and applying pharmacometric modelling and simulation in clinical practice and research. *Br J Clin Pharmacol*. 2017;83(2):247–254.
7. Neely MN, Kato L, Youn G, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62(2):e02042–e02017.
8. Joerger M, Von Pawel J, Kraff S, et al. Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2016;27(10):1895–1902.
9. van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M. Developing a paediatric drug formulary for the Netherlands. *Arch Dis Child*. 2017;102(4):357–361.
10. Brooks E, Tett SE, Isbel NM, Staatz CE. Population pharmacokinetic modelling and Bayesian estimation of tacrolimus exposure: is this clinically useful for dosage prediction yet? *Clin Pharmacokinet*. 2016;55(11):1295–1335.

11. Claisse G, Zufferey PJ, Trone JC, et al. Predicting the dose of vancomycin in ICU patients receiving different types of RRT therapy: a model-based meta-analytic approach. *Br J Clin Pharmacol*. 2019;85(6):1215–1226.

12. Zhang J, Zhou F, Qi H, et al. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared to body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. *Br J Clin Pharmacol*. 2019;85(10):2292–2301.

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